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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

. Office Action Summary	Application No. 09/729,264	Applicant(s) WELCHER ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *9,12-47,49-54 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11,48,55,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Not. to comply* .

DETAILED ACTION

Final Rejection

Claims 1-8, 10, 11, 48, 55, and 57-59 are pending.

Applicants' traversal, the amendment to claims 1-3, 48, and 57, the cancellation of claims 9, 12-45, 49-54 and 56, the addition of claim 59 in paper no. 20 filed on 4/2/03 is acknowledged and considered.

Information Disclosure Statement

The IDS filed on 4/2/03 is improper because there is no certification that the applicants were unaware of the references within 3 months of filing the IDS. A fee for the IDS was therefore charged as instructed in the IDS letter.

This application contains sequence disclosures (see new claim 59) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons set forth on the Notice to Comply. However, introducing new matter into a sequence list, e.g., by adding the sequence recited in claim 59 also would not comply with the sequence rules.

Claim Rejections - 35 USC § 112

Applicants' arguments, see paper no. 20, filed on, with respect to 112 written description have been fully considered and are persuasive. The rejection of claim 1 has been withdrawn because of the amendment to the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 59 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claim 59 filed on 4/2/03 introduces new subject matter into the application. The original specification did not disclose the nucleic acid sequences set forth in claim 59. The page cited (page 32 (Table I), page 35, lines 21-27 and Figures 1-7 and 9) for support of the added nucleotide sequence does not support the sequence. Page 32 is directed to a list of potential amino acid substitutions. Page 35, lines 21-27 contemplates comparing amino acid sequences with similar activity to B7-like polypeptide and identifying residues and portions of sequences that are conserved among similar sequences. Figures 1-7 are directed to human and murine B-7 like nucleotide sequences and Figure 9 is directed to comparing the human amino acid sequence to the murine amino acid sequence. Furthermore, applicants submit on 4/2/03 (appendix A) showing sequence comparison of several murine and human B7 like polypeptide that indicate the structural feature shared between these sequences. There is no evidence that the applicants were relying on the specification for their disclosure of the limitations in the nucleotide sequence in the newly added claim. It is apparent that the applicants at the time the invention was made did not intend or contemplate the isolated nucleic acid in claim 59.

In addition, the specification set forth a list of amino acids known to one skilled in the art. However, nothing in the specification would lead one to the particular combination set forth in claim 59. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997).

Claims 2, 3, 4-8, 10, 11, 48, 55, 57 and 58 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 3, 4-8, 10, 11, 48, 55, 57 and 58, as best understood, is readable on a genus of an isolated nucleotide sequence encoding a polypeptide fragment at least about 25 amino acid residues, wherein the polypeptide has an activity of a polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6, a genus of an isolated nucleic acid molecule comprising: a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6 with at least one amino acid substitution, deletion or modification, wherein the encoded polypeptide has an activity of a polypeptide as set forth in SEQ ID NO: 2, 4, or 6; wherein the genus of the claimed isolated nucleic acid molecules is not claimed in a specific biochemical or molecule structure that could be envisioned by one skilled in the art at the time the invention was made.

The specification contemplates a genus of an isolated nucleotide sequence encoding a polypeptide fragment at least about 25 amino acid residues, wherein the polypeptide has an

activity of a polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6, a genus of an isolated nucleic acid molecule comprising: a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6 with at least one amino acid substitution, deletion or modification, wherein the encoded polypeptide has an activity of a polypeptide as set forth in SEQ ID NO: 2, 4, or 6. The specification contemplates an isolated nucleic acid sequence having B7-like activity. However, the specification does not provide sufficient description of a genus of polynucleotide sequences that possess any activity of SEQ ID NO: 2, 4, or 6. The art of record displays that, "The B7 family of co-stimulatory molecules comprises B7.1 and B7.2 proteins, both of which can interact with two receptors, CD28 and CTLA-4, that are expressed by T cell proliferation, increasing evidence indicates that they may not deliver identical signals to T cells, and that they may skew Th1 and Th2 phenotypes" (Li et al. Human Immunology, Vol. 61: 486-498, 2000). The specification does not provide sufficient description of what activity is possessed by the claimed nucleotide sequences that are considered to have B7-like activity. There are two different B7 proteins with several different activities. The statement "polypeptide has an activity of a polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6" is not a predicate for the claims genus of sequences because an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of nucleotide sequences that must exhibit the disclosed biological functions as contemplated by the specification.

The as-filed specification does not provide an adequate written description of a representative number of species of nucleotide sequences, wherein said sequence has an activity

of SEQ ID NO: 2, 4, or 6. It is apparent from the state of the prior art exemplified by Ngo *et al.* (The Protein Folding Problem and Tertiary Structure Prediction, Birkhauser Boston, 1994, pp. 491-494) and Chiu *et al.* that the description of the primary sequence of amino acid residues in which the positions of the amino acid residues are particularly arranged is essential for the biological function of the protein encoded by the sequence. This essential element that is required for an adequate description of a representative number of species as embraced by the claimed genus of B-7 like encoded nucleic acid sequences is neither described sufficiently in the specification nor conventional in the prior art. A mere statement asserting that a nucleotide sequence, wherein the encoded polypeptide has **an activity** of the polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6 without providing the essential and specific arrangement of the amino acid residues positioned in the sequence does not lend evidentiary support for a skilled artisan to have recognized that applicants were in possession of the genus of B-7 like encoded nucleic acid sequences as broadly claimed, particularly since the essential element of the coding sequence of a generic B-7 like nucleic acid molecule having an activity of the polypeptide set forth in SEQ ID NO: 2, 4, or 6 is lacking from the as-filed specification and since the skill and knowledge in the art is not adequate or conventional to determine the primary sequence of the representative number of species of B-7 like encoded genes or nucleic acids on the basis of the only disclosure of B-7 like polypeptides encoded in SEQ ID NO: 1, 3 or 5.

Vas-Cath Inc. v Mhurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purpose of the 'written description' inquiry,

whatever is now claimed." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, See MPEP 2163).

The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or the simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v Chugai Pharmaceutical Co. Ltd., 18 USPQ 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification only provided the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997): *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement 'by describing the invention, with al it claimed limitations, not that which make it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Lockwood*, 107F.3d at 1572, 41 USPQ2d at 1966.

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmid and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Dir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. At 1170, 25 USPQ at 1606.

> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information, concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is not further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes; as the example does, does not necessarily describe the cDNA itself. No sequence information indication which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, the claimed invention provides sufficient description of isolated nucleic acid sequence encoding SEQ ID NO: 2, 4 or 6, but not an activity that is considered an activity of SEQ ID NOs: 2, 4, or 6 that would meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

Applicants' arguments filed 4/2/03 have been fully considered but they are not persuasive. The specification describes a nucleotide sequence as set forth in any of SEQ ID NO: 1, 3, or 5 and an isolated nucleic acid sequence encoding SEQ ID NO: 2, 4, or 6. However, the specification does not describe an activity of any of the claimed sequences or what amino acids are considered essential for an activity of SEQ ID NO: 2, 4, or 6. The specification does not describe relevant structural or physical characteristics of the claimed sequences. The specification does not describe the activities that the proteins are supposed to have. The specification contemplates that the sequences are B-7 like sequences, however, a sequence search indicates that none of the sequences are related to known B-7 sequences. Therefore, the

as-filed specification does not provide sufficient description of an activity from the amino acid sequence set forth in SEQ ID NO: 2, 4, or 6.

Claims 1-8, 10, 11, 48, 55, 57, 58 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the presently pending claims encompassing any isolated polynucleotides or polypeptide sequence encoding a B-7 like molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient description (for possessing a genus of a nucleotide sequence which hybridizes under at least moderately stringent conditions to the complement of the nucleotide sequence, wherein the nucleotide sequence has **an activity** of the polypeptide as set forth in any of SEQ ID NO: 2, 4, or 6 as recited in the claims, particularly in view of the reasons set forth above, one skilled in the art would not have known how to make and use the claimed invention so that it would operate as intended; e.g. method of modulating levels of B7-like polypeptide in an animal.

The claimed invention is an isolated polynucleotide sequence (SEQ ID NOs 1, 3, or 5) encoding a B-7 like molecule and the amino acid sequences encoding a B-7 like molecule (SEQ ID NOs 2, 4, or 6). The specification defines a B-7 like nucleic acid sequence (e.g. gene,

polypeptide, etc.) as comprising nucleotide sequence as set forth in 1, 3, or encoding SEQ ID NO: 2, 4, or 6 (pages 16-17). The as-filed specification encompasses determining the percent identity of the isolated nucleic acid molecule according to claim 2 using a computer program selected from GAP, BLASTP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.

Furthermore, with respect to claims 1-3, the claimed invention is not considered enabled because the specification does not provide sufficient guidance for one skilled in the art to use any of the claimed sequences because the specification does not provide a function for the claimed sequences or how the sequences are similar in activity to a nucleic acid encoding a B7 protein. In view of the breadth of the term "B-7 like", the specification does not provide sufficient guidance (e.g. BLAST search, functional assay, etc.) or evidence for one skilled in the art to reasonably determine that any of these sequences have an activity of a nucleic acid encoding B7. In addition, it is not apparent to one skilled in the art what biological properties consist of a B7-like molecule because the assertion that SEQ ID NO: 1-6 are most likely B-7 like nucleotides sequence does not provides sufficient guidance for one skilled in the art to use the nucleotide sequences and would result an undue amount of experimentation for one skilled in the art to use the nucleotide sequences. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the nucleotide sequence in many instances. The effects of these changes are largely unpredictable as to which mutation has a significant effect versus not. Therefore, the assertion of sequence similarity between the claimed sequences and B7 polypeptide without providing any guidance or evidence for the function of the claimed sequence results in an unpredictable and therefore

unreliable correspondence between the claimed sequences and the indicated similar sequences of known function and therefore lacks support regarding enablement. Several publications document this unpredictability of the relationship between sequences and function, albeit that certain specific sequences may be found to be conserved over sequences of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases: Gerhold et al., (Bioassays, Vol. 18, page 973-981 (1996), Russell et al., (Journal of Molecular Biology, Vol. 244, pages 332-350 (1994), and Wells (Journal of Leukocyte Biology, Vol. 61, pages 545-550, 1997).

In addition, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 23-228), it would require an undue experimentation for one skilled in the art to arrive at peptides that have B7-like activity. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify peptides that have B7-like activity, it certainty would require undue experimentation to make their corresponding DNA and, therefore claims 1-3 and 11 are not enabled.

In addition, the claimed invention contemplates using the isolated nucleic acid molecules of claim 1, 2, or 3 in a method of modulating levels of a polypeptide in an animal (claim 55). With respect to claim 55, at the time the application was filed the state of the art for gene therapy as exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, at the time the application was filed gene therapy was considered unpredictable

The as-filed specification contemplates several methods of gene therapy using the polypeptides and polynucleotides of the claimed invention. As stated above, it is not apparent to one skilled in the art what biological properties consist of a claimed B7-like molecule. The prior art recites that B-7, expressed on antigen presenting cells, provides a crucial co-stimulatory signal for T cell activation (Freeman et al., *J. Exp. Med.*, Vol. 178, 1993, pp. 2185-2191). The state of the prior art further displays that, "The B7 family of co-stimulatory molecules comprises B7.1 and B7.2 proteins, both of which can interact with two receptors, CD28 and CTLA-4, that are expressed by T cell proliferation, increasing evidence indicates that they may not deliver identical signals to T cells, and that they may skew Th1 and Th2 phenotypes" (Li et al). A sequence search of the prior art indicates that the closes related sequence is a novel human diagnostic protein (66.3 % identity, WO200175067, Drmanac et al.) with no similar function to a B7 protein. It is not apparent from the specification how the SEQ ID NOs: 1-6 are related to B-7 or what is a B7-like molecule as contemplated by the as-filed specification. Furthermore, the as-

filed specification does not provide sufficient guidance or evidence for how modulating levels of a B7-like polypeptide in an animal comprising administering to the animal the nucleic acid molecule of SEQ ID NOs: 1-6 correlates to a therapeutic effect in any animal. In addition, the breadth of the term "modulating" encompasses increasing or decreasing the level of the claimed nucleic acid molecule in an animal. One skilled in the art understands that a DNA sequence encoding a protein can be used to increase expression of that particular protein in a system (e.g. animal, in vitro cell). However, the as-filed specification fails to provide sufficient guidance or evidence for how one skilled in the art would be enabled to use the claimed nucleic acids to decrease the levels of B-7 like gene products in an animal. One skilled in the art understands that nucleic acid encoding a protein cannot be used to decrease the level of a gene product in a system and that one skilled in the art would use a nucleic acid molecule selected from an anti-sense molecule, ribozyme, etc. for decreasing the level of expression of a gene product in a system. Thus, in view of In re Wands Factors, it would take one skilled in the art an undue amount of experimentation to determine how to use the nucleic acid sequences (SEQ ID NOs: 1, 3, or 5) and/or the nucleic acid sequences encoding the polypeptide sequences (SEQ ID NOs; 2, 4, or 6) in any claimed method of modulating set forth in the claimed invention.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made do not enable one skilled in the art to use the claimed invention. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any animal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to how the biological function of any of the DNA molecules encoding a sequence (SEQ ID NOs 1-6) cited in the claims corresponds to a therapeutic effect in any animal,

one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed on 4/2/03 have been fully considered but they are not persuasive. The argument directed to page 93, lines 7-9 of the specification, where applicants teach that transgenic mice expressing B-7 like polypeptide exhibit seminal hyperplasia is not found persuasive. The art of record recites that B-7, expressed on antigen presenting cells, provides a crucial co-stimulatory signal for T cell activation (Freeman et al., *J. Exp. Med.*, Vol. 178, 1993, pp. 2185-2191). The state of the prior art further displays that, "The B7 family of co-stimulatory molecules comprises B7.1 and B7.2 proteins, both of which can interact with two receptors, CD28 and CTLA-4, that are expressed by T cell proliferation, increasing evidence indicates that they may not deliver identical signals to T cells, and that they may skew Th1 and Th2 phenotypes" (Li et al). A sequence search of the prior art indicates that the closest related sequence is a novel human diagnostic protein (66.3 % identity, WO200175067, Drmanac et al.) with no similar function to a B7 protein. It is not apparent from the specification how the SEQ ID NOs: 1-6 are related to B-7 or what is a B7-like molecule as contemplated by the claimed invention.

In addition, the art of record indicates that seminal vesicle hyperplasia in a transgenic mouse expressing SEQ ID NO: 14 is not considered a function of a B7 molecule. Furthermore, the B-7 like polypeptide is SEQ ID NO: 14 (223 base pairs, B71.m3), which is a murine sequence that is not listed in the claims. The specification does not teach or provide sufficient

guidance of factual evidence for how SEQ ID NO: 14 possesses the same function or amino acids as SEQ ID NOs: 2 (382 base pairs), 4 (386 base pairs), or 6 (386 base pairs).

With respect to the argument directed to claim 55. For the reasons set forth above, the specification does not describe how to the use the nucleotide sequences set forth in claims 1-3. The specification does not provide sufficient guidance or factual evidence for an activity of a B7-like polypeptide. Thus, one skilled in the art would not know how to use the nucleic acid molecule in claims 1, 2, or 3. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, with respect to the assertion that, "one with skill in the art could readily practice the claimed method using for example B7-like antisense inhibitors or dominant negative mutants identified by the genetic suppressor element screening approach disclosed in US Patents 5,217,889 and 5,811,234.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of gene therapy, for those skilled in

the art to experiment with the nucleic acid molecules in claims 1, 2, or 3, so as to modulate levels of a B7-like polypeptide as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what methods and/or materials are required for different claimed methods of gene therapy set forth in claim 55.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3, 8, 10, and 55 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "B7-like polypeptide" in claims 8, 10, and 55 is a relative term, which renders the claim indefinite. The term "B7-like polypeptide" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of a B7-like polypeptide are not defined by the specification. One skilled in

the art would look to the specification for the definition of a "B-7 like polypeptide" and the specification does not define the term. The specification defines that term as a SEQ ID NO: with no function or biological activity. Thus, the disclosure does not particularly point out and distinctly claim what is a "B-7 like polypeptide".

Applicants' arguments filed 4/2/03 have been fully considered but they are not persuasive. The argument is not persuasive because the definition of the term is circular.

Claim 3 recites the limitation "the encoded polypeptide". There is insufficient antecedent basis for this limitation in the claim.

Applicants' arguments filed 4/2/03 have been fully considered but they are not persuasive for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 remain rejected under 35 U.S.C. 102(a) as being anticipated by Marra et al. (The Washington University-NCI Mouse EST project, seq_name: gb_est82: BF040046, July 2, 1999). Marra discloses an EST sequence with nucleotides that are complementary to nucleotides

of SEQ ID NOs: 1, 3 or 5. In addition, the sequence taught by Marra is antigenic when administered to an animal. Thus, Marra anticipates the claimed sequences.

Applicants' arguments filed 4/2/03 have been fully considered but they are not persuasive. The sequence taught by Marra reads on a nucleotide sequence that is complementary to any of the claimed sequences. The specification does not define the term "complementary" or what % of a nucleotide sequence is considered to be complementary to the claimed nucleotide sequences. It is acknowledged that the Albert reference teaches a nucleotide sequence 5'A-G-C-T-A-G-C-T-3' is complementary to 5'-T-C-G-T-C-G-A-3'. However, the reference does not define what % of a nucleotide sequence is considered to be complementary to another nucleotide sequence. In view of Albert, the EST sequence taught by Marra is complementary to base pairs of the nucleotide sequence set forth in SEQ ID NOs: 1, 3, or 5.

To overcome the prior art anticipating the complement sequences, suggest amending the phrase "a nucleotide sequence that is complementary to the nucleotide of any of " to read as follows -- nucleic acid sequence that is the full complement of the nucleotide of any -- or -- the complement to the nucleotide sequence of --.

Claims 1-3 remain rejected under 35 U.S.C. 102(b) as being anticipated by Taudien et al. (NCBI [online] Bethesda, MD USA: United States National Library of Medicine [retrieved on 23 December 2002]. Retrieved from: NCBI, Accession Number AF121782). Taudien discloses a sequence that is complementary to the nucleotide sequences from SEQ ID NO: 1-6. In addition, the sequence taught by Taudien is antigenic when administered to an animal. Thus, Taudien anticipates the claimed sequences.

Applicants' arguments filed 4/2/03 have been fully considered but they are not persuasive. The sequence taught by Taudien reads on a nucleotide sequence that is complementary to any of the claimed sequences. The specification does not define the term "complementary" or what % of a nucleotide sequence is considered to be complementary to the claimed nucleotide sequences. It is acknowledged that the Albert reference teaches a nucleotide sequence 5'A-G-C-T-A-G-C-T-3' is complementary to 5'-T-C-G-T-C-G-A-3'. However, the reference does not define what % of a nucleotide sequence is considered to be complementary to another nucleotide sequence. In view of Albert, the EST sequence taught by Taudien is complementary to base pairs of the nucleotide sequence set forth in SEQ ID NOs: 1, 3, or 5.

To overcome the prior art anticipating the complement sequences, suggest amending the phrase "a nucleotide sequence that is complementary to the nucleotide of any of " to read as follows -- nucleic acid sequence that is the full complement of the nucleotide of any -- or -- the complement to the nucleotide sequence of --.

Conclusion

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Application No.: 09/729,264

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: Claim 59 recites a nucleotide sequence with no corresponding SEQ ID NO:. In addition, the sequence was not part of the paper copy and was not provided in computer readable form.

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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